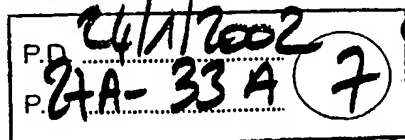


The 24-Hour Blood Pressure Pattern: Does It Have Implications for Morbidity and Mortality?



Michael A. Weber, MD

The onset of adverse cardiovascular events demonstrates a circadian pattern that reaches a peak in the morning shortly after awakening and arising. A parallel, 24-hour cyclical pattern has also been observed in the activities of various physiologic measurements, including blood pressure, heart rate, sympathetic nervous system activity, and platelet adhesiveness. Although a direct link has not yet been established, it can be postulated that the early morning surge in blood pressure may be a factor in precipitating acute cardiovascular episodes. Similar to the early morning blood pressure surge, blood pressure variability throughout the day appears to be a further independent risk factor for hypertensive target organ damage. Thus, it is reasonable to select an antihypertensive agent that offers smooth and well-sustained blood pressure control for the full 24-hour dosing interval, including the vulnerable early morning period. The results of clinical trials using ambulatory blood pressure monitoring have shown that

telmisartan, an angiotensin II receptor antagonist, possesses such properties. Whether or not these attributes of telmisartan might translate into improvements in cardiovascular morbidity and mortality will be explored in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This study will compare the effects of telmisartan 80-mg monotherapy, ramipril 10-mg monotherapy, or a combination of telmisartan 80 mg plus ramipril 10 mg, on cardiovascular endpoints in patients at high risk of cardiovascular events, several of whom are likely to be hypertensive at baseline. Inclusion of the telmisartan plus ramipril treatment arm will allow investigation of the potential advantages presented by combining an angiotensin-converting enzyme inhibitor with an angiotensin II receptor antagonist. ©2002 by Excerpta Medica, Inc.

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The existence of a circadian pattern of blood pressure has long been known but was first described in detail in the 1970s after continuous intra-arterial blood pressure monitoring of both normal and hypertensive ambulatory individuals.¹ These investigators reported that peak blood pressure levels occur during the mid-morning (at about 10:00 AM), then decrease progressively throughout the remainder of the day to reach a trough value the following morning at around 3:00 AM. A slow but steady increase in blood pressure is then observed over the early morning hours before awakening, with an abrupt and steep increase at approximately 6:00 AM, coincident with arousal and arising from overnight sleep. This morning blood pressure surge, from low nighttime levels to higher daytime levels, continues for 4 to 6 hours after awakening. Thus, variations in blood pressure, in general, tend to reflect the sleep-activity cycle.

The availability of automated, noninvasive, ambulatory blood pressure monitoring (ABPM) devices has allowed blood pressure to be measured safely and conveniently over a 24-hour period (typically at intervals of 15 to 20 minutes). The original intra-arterial observations by Millar-Craig et al¹ have been validated by investigations using ABPM, revealing a def-

inite and reproducible circadian pattern of blood pressure in most individuals.²⁻⁵

A circadian pattern of blood pressure is maintained among patients with essential hypertension, although there is an upward shift to the blood pressure curve throughout the entire 24-hour period compared with normotensive subjects, and the amplitude of the rhythm may be altered.⁶ In addition, some patients with hypertension do not exhibit a normal nocturnal decrease in blood pressure.^{7,8} Such individuals, sometimes described as "nondippers," are important clinically because they tend to exhibit more severe hypertensive target organ damage than their counterparts. This may be because of higher overall mean 24-hour blood pressure.⁹ Antihypertensive medication should, therefore, aim to provide full 24-hour control and preserve the normal nighttime decrease in blood pressure.

TIMING OF CARDIOVASCULAR EVENTS

Many cardiovascular events also demonstrate a circadian periodicity, with a peak incidence during the first few hours after awakening.^{2,10,11} This observation suggests a temporal association with the early morning blood pressure surge and other physiologic responses that occur on arising from overnight sleep.

Detection of transient ST-segment depressions by ambulatory electrocardiographic (Holter) monitoring has been used to examine whether myocardial ischemia follows a circadian variation during normal daily

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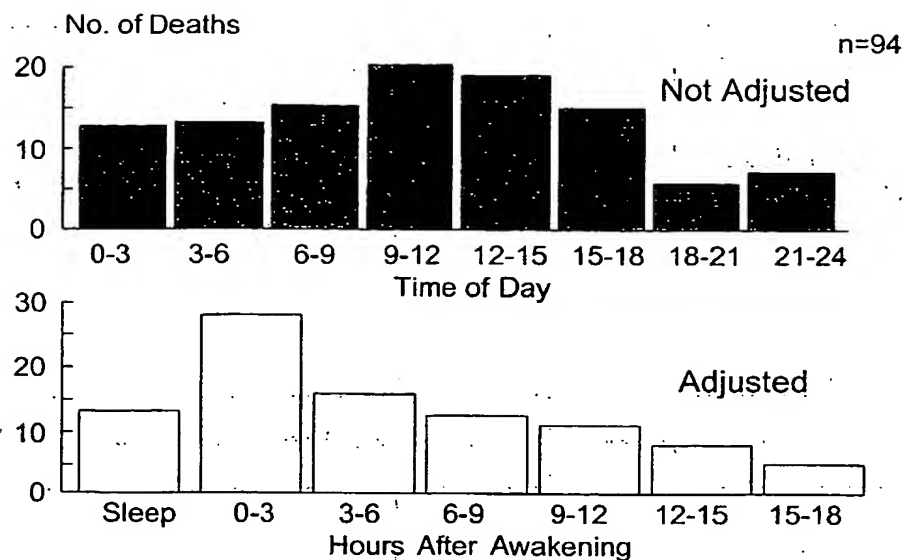


FIGURE 1. Circadian incidence of sudden cardiac death, adjusted for time of awakening. (Reprinted with permission from *Am J Cardiol.*²²)

activities.¹²⁻¹⁴ Such investigations have revealed an increased prevalence of ischemic attacks during the morning, with a strong clustering between 6:00 AM and 10:00 AM. Few episodes were detected during nighttime hours. A similar circadian distribution of episodes of myocardial ischemia was observed in an investigation, again using 24-hour ST-segment monitoring, of patients admitted to the coronary care unit with unstable coronary syndromes (acute myocardial infarction or unstable angina).¹⁵

Evidence also exists for a circadian pattern in the onset of myocardial infarction, with a disproportionate number of infarctions occurring during the hours after awakening. For example, in the Thrombolysis in Myocardial Infarction (TIMI) phase 2 trial, 34% of myocardial infarctions occurred between 6:00 AM and noon.¹⁶ Comparable results have been reported in other studies examining this phenomenon.^{11,17-20}

An uneven circadian distribution in the incidence of sudden cardiac death has likewise been reported. Analysis of mortality data from 5,209 patients in the original Framingham Heart Study database demonstrated a pronounced and significant ($p < 0.01$) circadian variation in the incidence of definite or possible sudden cardiac death.²¹ Again, a peak was noted during the morning, specifically between 7:00 AM and 9:00 AM, with the risk of sudden cardiac death estimated as being $\geq 70\%$ higher than at other periods during the day. Analysis of the time of sudden cardiac death in relation to the reported time of awakening showed that the highest proportion of events occurred within 3 hours of awakening (Figure 1).²² It has been postulated, although not proved, that sudden cardiac death is triggered by the physiologic processes that occur on awakening and is not merely a function of the time of day.

Finally, there appears to be a greater vulnerability to cerebrovascular accidents, including subarachnoid, ischemic, and hemorrhagic strokes, and transient ischemic attacks, over the morning hours.²³⁻²⁶ These findings should be interpreted with caution, because some individuals who have cerebrovascular events while they are sleeping will only become aware of them when they awaken the following morning.

THE UNSTABLE PLAQUE THEORY

The strong relation between the time of awakening from overnight sleep and the incidence of various cardiovascular events suggests that the physiologic responses related to arousal might trigger clinical outcomes. In addition to the early morning blood pressure surge, endogenous changes in other physiologic systems linked to the individual's sleep-activity cycle may contribute to the increased cardiovascular risk at this time of day.

First, the role of various neuroendocrine factors should be considered. Circulating catecholamine, renin, and cortisol concentrations are known to increase steeply during the morning waking hours,²⁷⁻²⁹ leading to an increase in vascular tone. In turn, constriction of the coronary vessels can be expected to predispose to myocardial ischemia in susceptible individuals. Catecholamines also exert positive inotropic and chronotropic effects on the heart, thereby potentially decreasing the threshold for life-threatening arrhythmias.

Second, the alterations in platelet activity and fibrinolytic status that occur during the morning hours are likely to heighten the tendency for thrombosis. A marked increase in platelet agglutinability has been reported between 6:00 AM and 9:00 AM²⁷ and has been linked to the assumption of an upright posture from a supine sleeping position.³⁰ In addition, tissue plasmin-

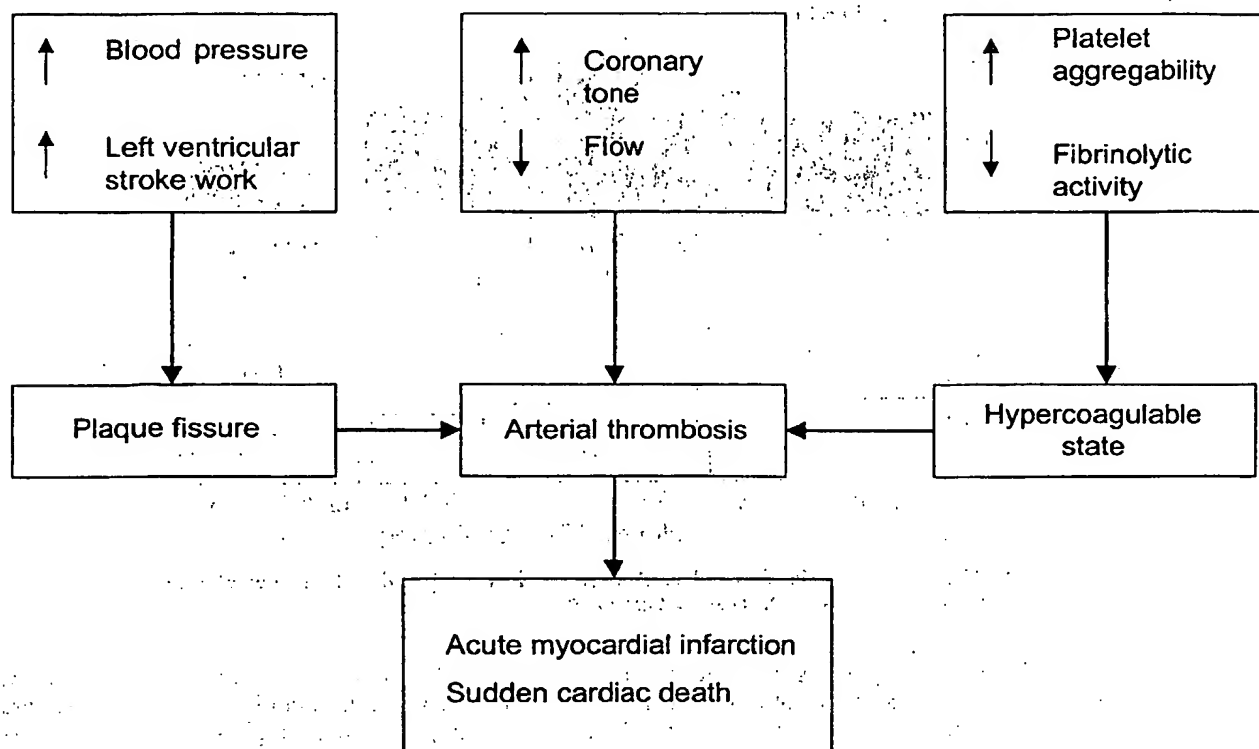


FIGURE 2. Potential adverse physiologic changes occurring during the morning waking hours and their association with cardiovascular events.

ogen activator and tissue plasminogen activator inhibitor-1 exhibit inverse circadian patterns such that fibrinolytic activity is at a trough during the morning.³¹ Increases in blood viscosity and hematocrit at this time of day further contribute to a prothrombogenic milieu.^{32,33}

A unifying mechanism, based on coronary artery thrombosis at the site of a ruptured atherosclerotic plaque, has been proposed to account for the excess cardiovascular risk associated with arousal from sleep among individuals with established cardiovascular disease (Figure 2).³⁴ The theory postulates that the blood pressure surge and the various vasoconstrictor responses that occur on awakening promote flow disturbances and dynamic changes in shear stress, resulting in the fissure of unstable atherosclerotic lesions. Exposed collagen in the fibrous cap of the plaque may trigger platelet adhesion and aggregation, leading to the formation of an occlusive thrombus and culminating in acute events, such as myocardial infarction, sudden cardiac death, or thrombotic stroke. The tendency for thrombosis is further heightened by concomitant increases in blood viscosity and a shift in fibrinolytic status toward a hypercoagulable state.

An alternative is the scenario in which the thrombus develops gradually, causing a reduction in blood flow, episodes of ischemia, microemboli, or even small necrotic foci. In this environment, any electrical

instability resulting from the morning increase in sympathetic activity may decrease the threshold for cardiac arrhythmias, especially among patients with left ventricular hypertrophy. The imbalance in myocardial oxygen demand and supply produced by the synergistic effects of humoral vasoconstrictor factors on the coronary arteries, together with the sudden acceleration in the rate-pressure product, may also reduce the threshold for myocardial ischemia.³⁵⁻³⁷ Finally, the excess of hemorrhagic strokes during the morning may be attributed to the surge in blood pressure at this time of day.

BLOOD PRESSURE VARIABILITY

ABPM has shown that blood pressure variability is an important determinant of target organ damage among patients with hypertension. A follow-up study of 73 hypertensive patients in whom a positive correlation had been previously demonstrated between 24-hour blood pressure variability and target organ damage has provided longitudinal evidence for this association.^{38,39} Subjects were arbitrarily divided into 4 groups according to their average 24-hour mean arterial pressure (<95 mm Hg, 95 to 108 mm Hg, 109 to 120 mm Hg, and >120 mm Hg). Each group was further subdivided according to whether the 30-minute standard deviation of blood pressure measurements (long-term variability) was above or below the aver-

age 30-minute standard deviation of the whole group. After a mean follow-up period of 7.4 years, the severity of target organ damage (a composite of several clinical observations) was found to be significantly greater in patients with blood pressure variability higher than average ($p < 0.01$). This association was observed in all 4 blood pressure subgroups.

Such results suggest that antihypertensive agents that minimize fluctuations in blood pressure, including blunting of the early morning surge, should be favored over those that do not offer consistent blood pressure effects over 24 hours.

EFFICACY OF 24-HOUR BLOOD PRESSURE CONTROL WITH TELMISARTAN

Because antihypertensive therapy should provide smooth, 24-hour blood pressure control with once-daily dosing, agents with long half-lives are preferred. Telmisartan is an angiotensin II type 1 (AT_1) receptor antagonist with a half-life of 24 hours, which is considerably longer than that of the other drugs in its class.⁴⁰ The efficacy of telmisartan for providing 24-hour blood pressure control has been tested extensively in several clinical trials using ABPM.⁴¹⁻⁴⁵ The results of these trials indicate that telmisartan lowers blood pressure significantly throughout the 24-hour dosing interval.

In 2 randomized, double-blind, placebo-controlled trials that used ABPM, the efficacy of telmisartan was compared with that of losartan or losartan plus hydrochlorothiazide for lowering blood pressure in patients with mild-to-moderate hypertension.^{43,44} In the first study, telmisartan 40 mg and 80 mg was associated with significantly greater mean reductions in systolic blood pressure and diastolic blood pressure than losartan 50 mg and placebo over the entire 24-hour dosing period and during the last 6 hours before dosing ($p < 0.05$).⁴³ In the second study, telmisartan 80-mg monotherapy and combination therapy with losartan 50 mg plus hydrochlorothiazide 12.5 mg were associated with similar reductions in mean systolic blood pressure and diastolic blood pressure during the 24-hour dosing period and during the last 6 hours before dosing.⁴⁴

Another telmisartan trial that used ABPM compared the 24-hour antihypertensive efficacy of telmisartan 80 mg with that of valsartan 80 mg.⁴⁵ In this study using these arbitrarily selected doses, telmisartan was associated with a significantly greater mean decrease in diastolic blood pressure during the last 6 hours before dosing and significantly greater reductions in systolic blood pressure and diastolic blood pressure during the daytime and morning periods than valsartan ($p < 0.01$).

The clinical trial database for telmisartan in which ABPM was used involved 2,651 patients with mild-to-moderate primary hypertension participating in 8 clinical trials. As such, this resource represents 1 of the largest ABPM clinical databases of any single AT_1 receptor antagonist. A meta-analysis of 5 of these studies (with a total of 1,566 patients) is under way.

The studies selected for the meta-analysis include 2 double-blind, placebo-controlled trials and 3 prospective, randomized, open-label, blinded-endpoint studies; the validity of combining ABPM data from these specific studies has been established (D.H.G. Smith, personal communication, January 2001). This meta-analysis will provide comparative data on the 24-hour efficacy of telmisartan, losartan, valsartan, amlodipine, and placebo. The preliminary findings are consistent with the results of the individual trials, indicating that telmisartan is a long-acting agent, because it is associated with significant antihypertensive efficacy throughout the 24-hour dosing interval, including the last several hours before dosing (D.H.G. Smith, personal communication, January 2001).

THE ONGOING TELMISARTAN ALONE AND IN COMBINATION WITH RAMIPRIL GLOBAL ENDPOINT TRIAL: A LOGICAL PROGRESSION FROM THE HEART OUTCOMES PREVENTION EVALUATION STUDY

The Heart Outcomes Prevention Evaluation (HOPE) study was designed to examine the capacity of angiotensin-converting enzyme (ACE) inhibitors to reduce major cardiovascular endpoints in patients at high cardiovascular risk.⁴⁶ Consequently, study patients had to have a documented history of myocardial infarction, interventional procedure for coronary artery disease, stroke, or peripheral arterial disease. Patients with diabetes plus an additional risk factor, such as hypertension, were also included. However, to differentiate HOPE from previous clinical trials, subjects with evidence of congestive heart failure or a reduced ejection fraction were not eligible.

The HOPE study comprised 2 treatment arms: ramipril titrated to a dose of 10 mg daily or matched placebo. Treatment was scheduled to continue for 5 years, but the trial was terminated prematurely (after a median of 4.5 years) because of a very clear reduction in the risk of cardiovascular death, myocardial infarction, and stroke in patients receiving ramipril.⁴⁷ The risk of a combined cardiovascular endpoint (comprising cardiovascular mortality, myocardial infarction, and stroke) was 22% lower among patients receiving ramipril than those receiving placebo ($p < 0.001$; Figure 3). Other important findings included a reduction of 26% in cardiovascular mortality, 20% in nonfatal myocardial infarction, 32% in stroke, 15% in the need for either coronary artery bypass grafting or angioplasty, and a 34% reduction in new-onset diabetes.

Only a moderate part of the benefit seen with ramipril in the HOPE study could be attributed to its effect on blood pressure; blood pressure measurements were not part of the formal observations in this study and thus may not have been reliable. Most subjects did not have hypertension at baseline, and the mean reduction in systolic blood pressure/diastolic blood pressure with ramipril was a modest 3/2 mm Hg, regardless of whether patients were hypertensive

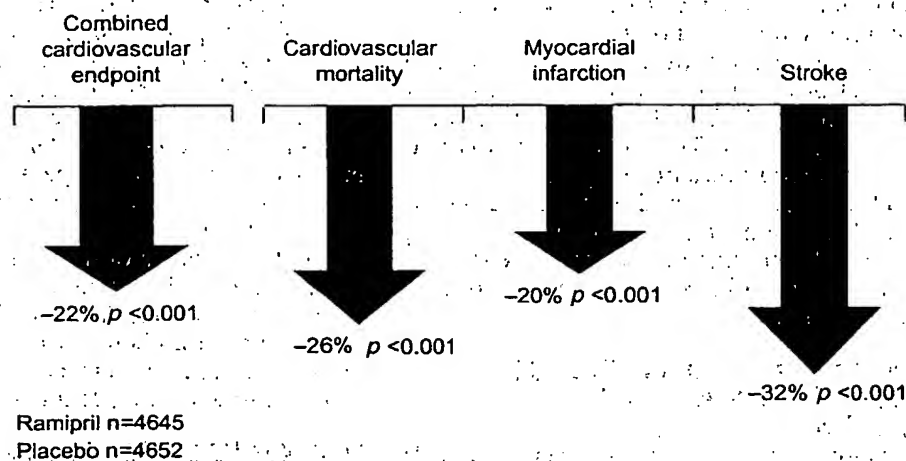


FIGURE 3. Relative risk reduction in cardiovascular endpoints with ramipril versus placebo in the Heart Outcomes Prevention Evaluation (HOPE) study. (Adapted from *Adv Ther*.⁴⁸)

or normotensive at baseline. The investigators estimated that this decrease in blood pressure might account for 40% of the risk reduction for stroke and 25% of the risk reduction for myocardial infarction.⁴⁷ Interestingly, an analysis of the HOPE study data according to baseline systolic blood pressure showed that the greatest reduction in cardiovascular risk was in patients who were hypertensive at baseline, despite the minimal effect on blood pressure (P. Sleight, personal communication, March 2001).

The most reasonable explanation for the higher than expected reduction in cardiovascular endpoints with ramipril among high-risk patients is that ACE inhibition confers cardiovascular protection through interruption of pathophysiologic processes associated with angiotensin II. These could include effects on vascular smooth muscle cell proliferation, endothelial dysfunction, left ventricular hypertrophy, vascular wall hypertrophy, atherosclerosis, glomerulosclerosis, and fibrinolysis. Because many of the detrimental activities of angiotensin II are mediated through the AT_1 receptor, treatment with a selective AT_1 receptor antagonist might offer similar cardiovascular benefits, especially as these blockers may interrupt the renin-angiotensin system more completely than ACE inhibitors. It is possible, too, that these improvements may even be augmented with AT_1 receptor antagonist treatment because of favorable effects resulting from stimulation of unopposed AT_2 receptors.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has been designed to test this hypothesis. Telmisartan was selected as the AT_1 receptor antagonist of choice, because a single daily dose provides smooth and sustained blood pressure control over the full 24-hour period between doses, including during the vulnerable early morning period,⁴¹⁻⁴⁵ and thus has the potential to add this hemodynamic benefit beyond its possible tissue protective effects. Furthermore, as with other

drugs in this class, telmisartan has a side-effect profile comparable to placebo.^{41,43,48-50} Patients enrolled in ONTARGET will be randomized to long-term, double-blind treatment with telmisartan 80-mg monotherapy, ramipril 10-mg monotherapy, or a combination of telmisartan 80 mg plus ramipril 10 mg. The primary endpoint will be a composite endpoint of cardiovascular mortality, stroke, acute myocardial infarction, and hospitalization for congestive heart failure.

Inclusion of a telmisartan plus ramipril treatment arm in ONTARGET allows exploration of the theoretical advantages on clinical outcome of combining an ACE inhibitor with an AT_1 receptor antagonist. It would be expected that the complementary mechanisms of action of these 2 drugs would produce more complete blockade of the renin-angiotensin system. In turn, this should provide greater hemodynamic control, and potentially additive cardiovascular, renal, and metabolic protective effects. Furthermore, the putative tissue protective properties associated with increased bradykinin levels (resulting from ACE inhibition) should be preserved.

CONCLUSION

The recognition that the onset of cardiovascular events follows a circadian pattern, and that it might even be triggered by the physiologic processes associated with awakening and arising from sleep, has prompted a reassessment of treatment approaches. The postulated role of the early morning blood pressure surge in precipitating such events would support the use of antihypertensive agents that confer blood pressure control throughout the hours immediately before and after awakening. Because many patients incorporate therapy administration into the routine activities associated with getting up in the morning, the peak incidence of cardiovascular events and the early morning surge in blood pressure unfortunately

will coincide with the end of the dosing intervals when drugs have their least pharmacologic effects. Thus, blood pressure control during the vulnerable post-awakening period will be dependent on the persistence of pharmacodynamic activity of the dose taken the previous morning, indicating the preferential selection of antihypertensive agents with long durations of action and proven efficacy over the entire 24-hour interval between doses.

The ONTARGET study should help to determine whether full 24-hour blood pressure control, as provided by telmisartan, has a beneficial impact on cardiovascular morbidity and mortality beyond the drug's blockade of other angiotensin II actions. Indeed, this trial should contribute to our understanding of the role of the renin-angiotensin system in cardiovascular disease. Of particular interest is whether more complete blockade of this physiologic axis with a combination of an ACE inhibitor and an angiotensin II receptor antagonist will translate into even greater improvements in clinical outcome than those observed in the HOPE study, which were associated with ACE inhibition alone.

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DISCUSSION

Question: What outcome would you predict from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)?

Michael A. Weber, MD (New York, New York, USA): Of course, none of us can say. However, adding an angiotensin II type-1 receptor blocker to an angiotensin-converting enzyme inhibitor should provide complementary benefits. With more complete

blockage of the renin-angiotensin system, we may see improved hemodynamic control, particularly at the end of the dosing interval. Cardiac, renal, and metabolic improvements may also be increased with combination therapy. Although I cannot predict the patient outcome, I am certain that we will learn a great deal from the study and that this monumental effort will be very rewarding.



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